

Formulation and *in vitro* evaluation of a fast-disintegrating/sustained dual release bucoadhesive bilayer tablet of captopril for treatment of hypertension crises

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Abstract

Hypertension crisis is one of the main health problems and its effective treatment is of high importance. For this purpose, fast-disintegrating and sustained release formulations of captopril, as a drug of choice, were prepared using conventional mucoadhesive polymers hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (Na-CMC), hydroxypropyl cellulose (HPC), Carbopol 934 (CP934) and sodium alginate (Na-alg). The optimum sustained release formulations were selected based on mean dissolution time (MDT). The swellability and mucoadhesive properties of selected formulations were assessed and compared. A direct relationship between swelling and release rates/adhesiveness of sustained release formulations was observed. The results showed that formulations containing combination of CP934 and cellulose-based polymers had the highest swellability, sustainability and adhesion strength. These formulations prolonged drug release up to 8 h showing good fitness to Korsmeyer-Peppas model. Moreover, the adopted fast-disintegrating tablet could release up to 100% of drug within 3 min in oral pH. Finally, a dual fast-disintegrating/sustained release bucoadhesive bilayer tablet consisting of optimized formulations was prepared releasing 30% of the drug initially within 15 min and the remaining up to 8 h which could be considered as an appropriate formulation for the treatment of hypertension crises.

Keywords: Bilayer; Captopril; Dual release; Fast-disintegrating; Sustained release; Bucoadhesive.

INTRODUCTION

Modified release drug delivery systems have attracted a great deal of interest in recent decades. In the field of oral drug delivery, one of the main factors determining the extent of absorption and duration of effect is the time that drug is present in the site of absorption (1). Modified release drug delivery systems alter the time course of drug release and/or retain the system at the site of absorption for a longer period of time (2). The former strategy has been commonly utilized in the sustained release dosage forms while the later can be achieved by mucoadhesive or GI-retentive formulations. For drugs which have a narrow absorption window, it is crucial to retain the drug in its absorption site with a sustained release manner to achieve maximum extent of

absorption and also not to saturate the carrier-mediated transport when the mechanisms other than passive diffusion are present (3).

Captopril is an oral antihypertensive drug and a member of angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors are considered for treating high blood pressure, heart failure, and prevention of kidney failure due to hypertension and diabetes (4). Short biological half-life of 1-2 h is one of the most important drawbacks of captopril requiring frequent administration of the drug which leads to poor patient's compliance. In addition, captopril has narrow absorption window in duodenum which limits its absorption from other parts of the intestine (5). In order to overcome these shortcomings, many attempts

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have been made by researchers to develop systems which are able to prolong drug release and/or to retain the system in the upper parts of GI tract. These approaches include floating tablet (6), floating beads (7), mucoadhesive systems (8,9), pulsatile release dosage forms (10), sustained release formulations such as osmotic pumps (11) and oily semisolid matrices (12). Amongst all, bioadhesive GI-retentive drug delivery systems which localize a delivery device within the lumen and enhance the bioavailability of drugs have attracted more attention (2).

This approach frequently involves the application of bioadhesive and swellable polymers such as pectin (13), sodium alginate (Na-alg) (14,15), sodium carboxymethyl cellulose (Na-CMC) (16), hydroxypropyl methylcellulose (HPMC) (17), chitosan (18,19), tragacanth (20) and acrylate polymers like polyacrylic acid (known as Carbopol) (21). Some factors including the medium in which the polymer is swelled, physiological properties of adhesion site and other physiochemical properties such as molecular weight of the polymer, chain flexibility, hydrogen binding capacity, cross-linking density, electrical charge, concentration, and hydration capacity of the polymer affect mucoadhesion strength of the dosage form (22).

With regard to the drawbacks of captopril including short half-life and narrow absorption window, a sustained release mucoadhesive drug delivery system would be beneficial. Besides, captopril is the drug of choice in the management of hypertension crises. Also, some authors have indicated efficient absorption of captopril from buccal cavity (23,24) and therefore, captopril conventional immediate release tablets are applied to the oral cavity by caregivers for urgent control of hypertension (4). However, these dosage forms may not be able to release the drug quickly and completely in oral cavity due to formulation limitations. In addition, no orally disintegrating or sublingual dosage forms have so far been specifically designed for this purpose.

Therefore, the aim of the current study was to develop and evaluate a bilayer dual release

tablet comprising a fast-disintegrating layer for quick release of the drug to control hypertension crisis and a bucoadhesive sustained release layer to adhere to oral cavity and release the drug for a longer period of time.

MATERIAL AND METHODS

Materials

Captopril and crospovidone (CPVP) were kindly donated by Exir Pharmaceutical Co. (Iran). HPMC (K 100 M) and Avicel® were supplied by Darupakhsh Pharmaceutical Co. (Iran). Magnesium stearate (MgS), Na-CMC and mannitol were purchased from domestic suppliers of Merck Co. (Germany). Carbopol 934 was purchased from domestic suppliers of BF Goodrich Co., (USA) and Na-alg was purchased from Sigma-Aldrich Co. (USA). All other materials were reagent grade and used without further modification.

Captopril UV analysis

Captopril was quantified using spectrophotometric method at 205 nm (Shimadzu, UV-1650PC, Japan). The procedure was repeated in three different days and validation parameters including accuracy, precision and linearity were determined. In order to rule out the excipients interference, a blank of each formulation was prepared and was scanned in range of measurement (200–400 nm).

Preparation of captopril fast disintegrating and sustained release tablets

In this study, two series of sustained release tablets were prepared. The first ones were prepared using a single polymer at 25, 50 or 75% w/w, while in the second series CP934 or Na-alg along with one cellulosic polymer was incorporated in the tablet formulation and lactose was used as the filler. Captopril tablets were prepared by mixing captopril (50 mg) with appropriate quantity of polymer(s), MgS (1 % w/w) and lactose. The powder mixtures were directly compressed by a single punch tableting machine with a 9 mm diameter flat plain punch (Erweka, AR400, Germany). The weight of tablets was set at 240 mg. The hardness of prepared tablets was adjusted

between 5 to 6 kg (Erweka hardness tester, Germany). The composition of formulations prepared is summarized in Table 1. Formulations which were able to release more than 80% of their drug content within 60 min were chosen for preparing the fast dissolving layer. To optimize the release behavior, the effect of addition of 5% w/w crospovidone on drug release rate was studied. In the case of sustained release formulations, formulations releasing more than 80% of their drug content within 4-8 h were selected as sustained release layer of the formulations.

In vitro dissolution and release studies

Captopril release from different formulations was determined using USP type I dissolution apparatus (basket apparatus, Erweka, DT70, Germany) under sink condition at 100 ± 2 rpm. The dissolution medium was consisted of 500 mL phosphate buffer USP pH 6.8 (to simulate oral cavity fluids) maintaining at 37 ± 0.5 °C. The prepared formulations were subjected to dissolution test for 8 h. The samples (5 mL) were withdrawn at predetermined time intervals of 2.5, 5, 7.5, 10, 15, 30, 60, 90, 120,

180, 240, 360 and 480 min and replaced by an equal volume of the same dissolution medium. The amount of drug released from tablets was determined by a validated UV-Visible spectrophotometric method at 205 nm. Captopril conventional tablets, from two Iranian companies (Exir and Darupakhsh) were used as standard to compare their release profile with prepared fast disintegrating tablets. All experiments were carried out in triplicate and average values and standard deviations were calculated.

Release kinetic analysis

In order to investigate the release mechanism of captopril from sustained release matrices, various kinetic models including zero order, first order, Higuchi, and Korsmeyer–Peppas models were considered.

Mean dissolution time (MDT) was calculated from release data using equation 1 (25).

$$MDT = \frac{\int_0^{\infty} t \cdot W_d(t) \cdot dt}{\int_0^{\infty} W_d \cdot dt} \quad (1)$$

where, W_d is the cumulative amount of drug released at time t .

Table 1. The composition of sustained release and fast-disintegrating tablets of captopril (mg per each tablet).

Polymeric formulations	Na-alg.	CP934	HPMC	Na-CMC	HPC	Mannitol	Avicel®	Lactose	CPVP
F1	60	-	-	-	-	-	-	130	-
F2	120	-	-	-	-	-	-	70	-
F3	180	-	-	-	-	-	-	10	-
F4	-	60	-	-	-	-	-	130	-
F5	-	120	-	-	-	-	-	70	-
F6	-	180	-	-	-	-	-	10	-
F7	-	-	60	-	-	-	-	130	-
F8	-	-	120	-	-	-	-	70	-
F9	-	-	180	-	-	-	-	10	-
F10	-	-	-	60	-	-	-	130	-
F11	-	-	-	120	-	-	-	70	-
F12	-	-	-	180	-	-	-	10	-
F13	-	-	-	-	60	-	-	130	-
F14	-	-	-	-	120	-	-	70	-
F15	-	-	-	-	180	-	-	10	-
F16	-	60	60	-	-	-	-	70	-
F17	-	60	-	60	-	-	-	70	-
F18	-	60	-	-	60	-	-	70	-
F19	60	-	60	-	-	-	-	70	-
F20	60	-	-	60	-	-	-	70	-
F21	60	-	-	-	60	-	-	70	-
F22	-	-	60	-	-	-	-	118	12
F23	-	-	60	-	-	-	118	-	12
F24	-	-	-	-	-	-	-	190	-
F25	-	-	-	-	-	190	-	-	-

Swelling study

For this purpose, the formulations which released more than 80% of their drug content in 4-8 h were analyzed. The tablets were immersed in phosphate buffer solution (5 mL) and removed at predetermined time intervals of 30, 60, 120, 180, 240 and 360 min. The swollen tablets were weighed after absorbing their surface water by filter paper and swelling percent was calculated using following formula (26).

$$\text{Swelling \%} = [(W_t - W_0)/W_0] \times 100 \quad (2)$$

where, W_t is the weight of tablet at time t and W_0 is the initial weight of the tablets.

Adhesion study

There are different methods to measure the adhesive properties of a formulation which are almost based on the measurement of the force required to separate formulation from a smooth surface. In the current study an apparatus designed in our laboratory was used to measure the adhesion strength of the tablets (27). Measurements were performed on the formulations that showed over 80% drug release within 4-8 h. Each measurement was repeated four times and average values were reported in g/cm^2 .

Preparation of bilayer dual release tablet

The optimum fast disintegrating formulation was reformulated to contain one-third of total tablet weight containing 12.5 mg captopril. The rest of tablet weight (two-third) consisted of sustained release layer containing 37.5 mg captopril. The bilayer tablet was also prepared by direct compression as mentioned in previous section.

Data analysis method

One-way ANOVA with Tukey post hoc test using SPSS software version 18 was utilized to analyze spectrophotometric and adhesion data. The confidence limit was set at 95% and 80% power was considered for interpretation of the results.

RESULTS

Validation of captopril quantification method

Quantitative determination of captopril in dissolution medium was performed using a UV-visible spectrophotometer. The calibration curve of captopril in phosphate buffer (pH 6.8) showed a linear relationship in the range of 5-25 $\mu\text{g/mL}$ ($R^2 = 0.999$). The accuracy and CV% of the method were 98.2% and 0.04%, respectively. In addition, the scanning of the blank solutions of tablets with no drug showed no remarkable interference to drug measurements.

Evaluation of drug release

In the present study, formulations which released more than 80% of their drug content within 4-8 h were considered as sustained release formulations and those showing highest release percent in the first 15 min were selected as fast disintegrating formulations.

Captopril conventional tablets are immediate release formulations and ones studied here released up to 90.2% (for Exir pharmaceutical company, Iran) and 83.1% (for Darupakhsh pharmaceutical company, Iran) of their drug within 15 min meeting the dissolution requirements stated in USP for immediate-release captopril tablets (Fig. 1).

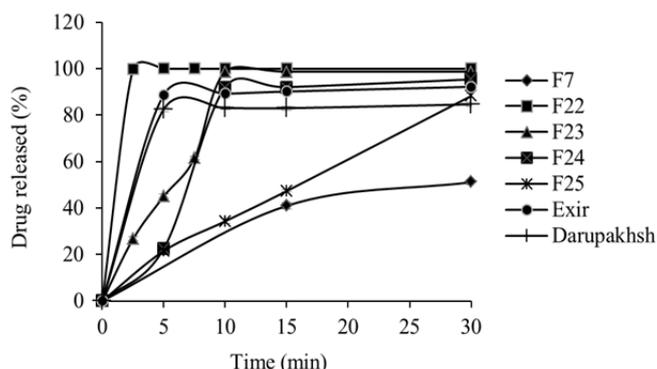


Fig. 1. Drug release profiles of polymeric and polymer-free fast disintegrating formulations ($n = 3$).

The effect of filler on the extent and rate of drug release in the absence of polymer was investigated. Formulations F24 and F25 containing lactose and mannitol respectively, released up to 95% and 88.3% of their drug within 30 min. Release rate from F24 was two times higher than F25 in early 15 min (92.1% vs. 47.4%) as presented in Fig. 1. Therefore lactose was selected as suitable filler (Fig. 1).

Amongst single polymer-containing matrices, F7 showed over 40% drug release within 15 min. Therefore F7 formulation was selected as fast disintegrating formulation (Fig. 1) and the effects of CPVP and Avicel® on release profile of captopril from F7 were studied.

When 5% CPVP was added to the F7 formulation (designated as F22) almost complete release of loaded drug (100%) was achieved within 5 min (Fig. 1). Although Avicel® is an effective disintegrant, incorporation of it in formulation F23 had no positive effect on release profile (Fig. 1) Hence, F22 was selected as fast disintegrating formulation for preparation of bilayer dual release tablet. Formulations F1 and F2 (25% and 50% Na-alg), F4 (25% CP934), F9 (75% HPMC), and all HPC-containing formulations (F13, F14 and F15) released their captopril content in a sustained manner within 4-8 h (Fig. 2A). These formulations were selected for further investigations.

Formulations containing combination of two mucoadhesive polymers showed more sustaining effect. Generally, in comparison with Na-alg based combination formulations, CP934 incorporated formulations demonstrated higher retarding capability. With exception of F20 which showed incomplete drug release of about 75% in 8 h, the remaining formulations were able to release over 80% of their payload within 4-8 h (Fig. 2B).

The time needed for the release of 25% ($t_{25\%}$), 50% ($t_{50\%}$), and 75% ($t_{75\%}$) captopril from different sustained release formulations was determined (Table 2). Formulations containing CP934, alone (F4) or in combination with other polymers (F16, F17 and F18) required longer time to release 75% of the drug.

According to the literature, the risk of dose dumping is higher in sustained release formulations showing over 30% drug release in the first hour of dissolution (28). Based on the obtained results, the possibility of dose dumping for F1, F15 and F16 formulations are very low.

Retarding capability of a polymer to prolong drug release from a dosage form is characterized by MDT value. As demonstrated in Table 2, formulations prepared with combination of two polymers showed higher MDT values.

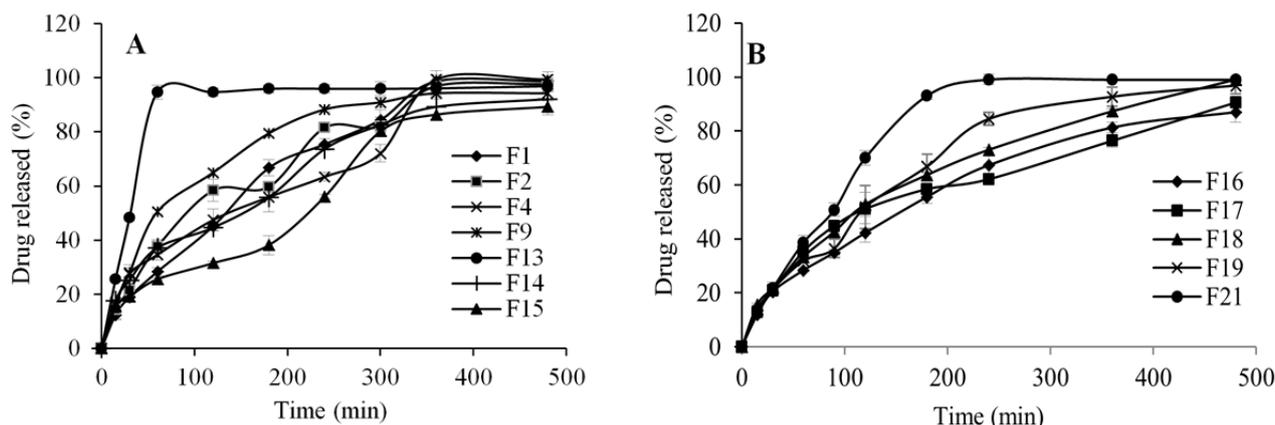


Fig. 2. Captopril release profiles from (A) single polymer, (B) two-polymer containing formulations which released over 80% of captopril within 4-8 h (n = 3).

Table 2. Time to release specified amount of captopril from sustained release formulations and corresponding MDT values*.

Formulations	t _{25%} (h)	t _{50%} (h)	t _{75%} (h)	MDT (h)
F1	0.72 ± 0.15	1.54 ± 0.11	3.00 ± 0.10	2.00 ± 0.10
F2	0.54 ± 0.13	1.55 ± 0.12	2.86 ± 0.11	1.95 ± 0.80
F4	0.47 ± 0.12	1.83 ± 0.16	4.09 ± 0.22	2.31 ± 0.12
F9	0.41 ± 0.13	1.00 ± 0.09	1.89 ± 0.14	1.57 ± 0.10
F13	0.25 ± 0.07	0.55 ± 0.08	0.92 ± 0.10	0.74 ± 0.05
F14	0.50 ± 0.15	1.66 ± 0.12	3.39 ± 0.13	2.35 ± 0.17
F15	1.00 ± 0.08	2.47 ± 0.18	3.93 ± 0.26	2.94 ± 0.18
F16	0.77 ± 0.03	2.57 ± 0.15	5.20 ± 0.22	3.23 ± 0.19
F17	0.55 ± 0.14	2.57 ± 0.19	5.19 ± 0.31	3.16 ± 0.12
F18	0.68 ± 0.18	1.91 ± 0.14	4.04 ± 0.25	2.59 ± 0.11
F19	0.69 ± 0.17	2.06 ± 0.17	3.45 ± 0.18	2.36 ± 0.17
F21	0.60 ± 0.14	1.50 ± 0.13	2.29 ± 0.19	1.47 ± 0.12

*All values represent mean ± SD (n = 3).

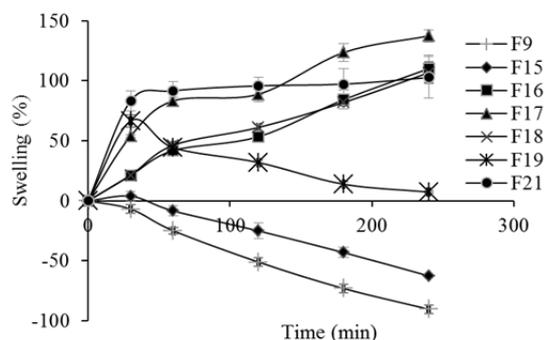


Fig. 3. The swelling profiles of sustained release formulations showing MDT values longer than 2.5 h (n = 5).

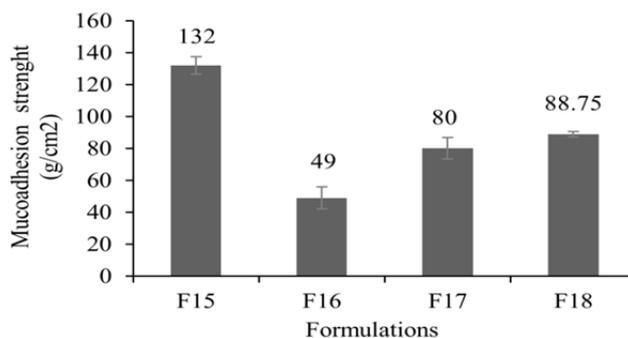


Fig. 4. The adhesion strength of sustained release formulations having MDT values of longer than 2.5 h (n = 4).

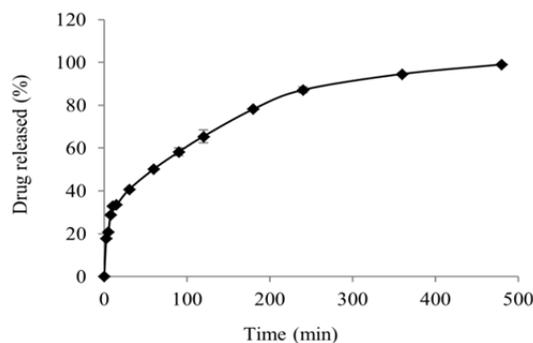


Fig. 5. Drug release profile of dual release bilayer tablet containing a fast disintegrating (F22) and a sustained release layer (F17) in phosphate buffer pH 6.8 (n = 3).

Release kinetics

Different kinetic models were employed to investigate the release mechanism of captopril from sustained release matrices. Based on the results, more consistency was observed with Korsmeyer–Peppas model. Since cylindrical geometry is considered the most suitable shape explaining release kinetic behavior of matrix tablets, the release exponent must be equal or below 0.45 for Fickian (case I) transport, between 0.45-0.89 for anomalous or non-Fickian transport, and equal or higher than 0.89 for super case II type of drug release. Generally, while super case II refers to the erosion of the polymer, both diffusion and erosion play role in anomalous transport (29).

In all experiments the release exponent values laid between 0.45-0.89 indicating both diffusion and erosion involved in drug release from sustained release tablets.

Swelling study

Fig. 3 represents the matrix swelling (%) as a function of time. As depicted, F16, F17, F18, and F21 had positive swelling along time. According to the results of the release kinetic, in all formulations there is a high agreement with Korsmeyer–Peppas model as the mechanism of release. Therefore, it is obvious that the matrices underwent both swelling and erosion at the same time after placement in the dissolution media and negative swelling is obvious in some formulations (Fig. 3).

Adhesion study

Fig. 4 illustrates the adhesion strength of the sustained release matrices made of single or combination of polymers with MDT values higher than 2.5 h. As depicted, formulation F15 showed the highest adhesion strength ($132 \pm 5.45 \text{ g/cm}^2$). According to the results, the adhesion strength for selected two-polymer containing formulations can be ranked as follow: F18 > F21 > F17 > F19. An interesting finding was that the combination of CP934 and Na-alg with cellulose-based polymers resulted in highly adhesive matrices showing an inter-chain interaction of polymers. Our previous experience about prednisolone bucoadhesive tablets showed similar behaviour (27). Since F17 showed longer MDT and

acceptable adhesion strength of 80 g/cm^2 , it was selected as the best formulation for preparation of bilayer tablet.

Captopril bilayer dual release tablets

Drug release profile of the bilayer dual release tablet (Fig. 5) demonstrated that 30% of captopril (15 mg) released in early 15 min and the remaining 70% of drug (35 mg) was released up to 8 h.

DISCUSSION

CPVP is a superdisintegrant which has been extensively used to formulate fast disintegrating or oral disintegrating tablets (30). Therefore, in current study, beside water soluble polymer (HPMC) and excipients (mannitol, lactose and Avicel®), CPVP was used as an efficient superdisintegrant polymer which significantly increased the rate of drug release. This observation can be explained by the ability of CPVP for rapid swelling and facilitating drug release from matrices with lack of sufficient swelling and drug release (23). In addition, according to the results, lactose replacement with Avicel® reduced the rate of drug release. This effect can be ascribed to the fact that unlike Avicel® which is a water-insoluble cellulose derivative, lactose is a water-soluble filler which helps fast hydration of drug, dilution of the gel layer, faster gel erosion and faster release (31).

Cellulosic polymers (HPMC, HPC and Na-CMC), CP934 and Na-alg are vastly available which were used in the current study. In contrast to hydrophobic matrices, the diffusion process is not the only mechanism affecting release of the drug from hydrophilic matrices. As Bamba *et al.* (32) and Capan *et al.* (33) proposed, the release pattern of a drug from the formulation is fitted to a first-order kinetic equation, the underlying rate limiting steps in drug release could be water permeation, gelation rate and diffusion rate of drug in the gel. If the release is governed by porous penetration, the Higuchi model should be fitted. Moreover, Pappas *et al.* and Sahlin (34) stated that polymer dissolution (erosion) is another phenomenon which greatly influences drug release from hydrophilic swellable

matrices. Therefore, in such systems dual release mechanisms exist, polymer erosion following polymer relaxation as a result of swelling and diffusion of drug through the gel layer. These complex mechanisms of release can be explained by Korsmeyer-Peppas model. The diffusional exponents of the Korsmeyer-Peppas model were in the range of 0.45-0.89 which is indicative of anomalous transport and the influence of swelling and erosion on drug release.

According to the results, the polymer content was the most important factor controlling drug release rate. The higher polymer content accompanied with the longer MDT (F13, F14 and F15) which can be attributed to smaller micropores and increased tortuosity (25). Sufficient swelling is also a prerequisite for mucoadhesion. It has been shown that higher mucoadhesion strength is associated with the formulations with higher swelling properties (35).

In the present study, matrices with higher swelling indices indicated stronger adhesion (F17 > F16 > F18). As Peppas and Buri (36) have discussed, the bioadhesion mechanism can be defined as chemical and physical processes.

The chemical mechanisms describe the importance of chemical interaction between functional groups on bioadhesives. Accordingly, polymers containing hydroxyl and carboxyl groups are the best candidates for bioadhesive formulations (36). Na-CMC and Carbopol are acidic polymers with carboxyl groups on their surfaces (pKa 4.3 and 5.5, respectively). Therefore, at pH values of 1 unit higher than their pKa, they are almost in ionized state. Ionization enables them to swell more efficiently and form strong ionic or hydrogen binding interactions with mucin proteoglycans leading to stronger mucoadhesion.

On the other hand, these matrices showed longer MDT values which make them suitable as a sustained release dosage form. Higher degree of ionization produces larger swollen gel-like matrices with more tortuosity and longer diffusion path which in turn reduces the rate of drug release and increases the MDT value.

From a clinical view point, as Castro del Castillo *et al.* have stated, a sublingual 25 mg dose of captopril is the minimum effective dose and it is also possible to administer 12.5 mg as sublingual at 10 to 15 min intervals up to a maximum dose of 37.5 mg as an alternative treatment in hypertensive crisis (37). Therefore, a bilayer tablet comprising a fast disintegrating layer and a sustaining layer containing 12.5 and 37.5 mg captopril, respectively, was prepared. The bilayer tablet released 30% (15 mg) captopril within 15 min (12.5 mg in early 2.5 min) and remaining 70% (35 mg) within 8 h. This release pattern fulfills the need to a fast effective initial dose for quick reduction of blood pressure and a sustained dose maintaining the effect up to 8 h to prevent a recurrent hypertension crisis. In addition, the mucoadhesive nature of the dosage form makes it suitable for sublingual or buccal administration.

CONCLUSION

Preparation of a bilayer fast-disintegrating/sustained release mucoadhesive tablet of captopril was performed to preclude the limitations and drawbacks of conventional formulations in management of both hypertension and its crises. The fast disintegrating tablet of choice exhibited almost complete drug release within 3 min in oral gastric pH.

The optimized sustained release formulation showed a drug release up to 8 h following Korsmeyer-Peppas kinetic model. The dual fast-disintegrating/sustained release buccoadhesive bilayer tablet was able to release 30% of drug in the first 15 min and continued to release the remaining drug within 8 h which fulfill the requirement for optimized management of hypertension crises and recurrence prevention. Due to appropriate swelling and adhesions properties, the tablet could be retained in oral cavity or upper GI tract releasing its drug content in a sustained manner. Direct compression technique used to prepare this bilayer tablet is cost effective enabling pharmaceutical industries to commercialize the product by available facilities.

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REFERENCES

- Omidian H, Park K. Oral targeted drug delivery systems: gastric retention devices. In: Wen H, Park K, editors. Oral controlled release formulation design and drug delivery: Theory to practice. New Jersey: Wiley; 2010. pp. 185-204.
- Davis SS. Formulation strategies for absorption windows. *Drug Discov Today*. 2005;10(4):249-257.
- Hoffman A, Stepensky D, Lavy E, Eyal S, Klausner E, Friedman M. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. *Int J Pharm*. 2004;277:141-153.
- Cardiovascular Drugs, Captopril. In: Sweetman SC, editor. Martindale the complete drug reference. 36 ed. London, Chicago: Pharmaceutical Press; 2009. pp. 1239-1240.
- Gabor F, Fillafer C, Neutsch L, Ratzinger G, Wirth M. Improving oral delivery. In: Schäfer-Kortin M, editors. Drug delivery. Berlin: Springer; 2010. pp. 345-398.
- Rad T, Mortazavi S, Z Jafari-Azar R. Formulation and evaluation of captopril floating matrix tablets based on gas formation. *Res Pharm Sci*. 2012;7:S339.
- Thadkala K, Perma Kumari NP, Prathyusha R, Raju A. Formulation development, optimization and characterization of floating beads of captopril. *Int J Pharm Res Allied Sci*. 2013;2:32-46.
- Kumar M, Dhiman S, Johari N, Nanda A, Sahoo PK. Formulation, optimization and evaluation of gastritretentive mucoadhesive microspheres of captopril. *Indo Am J Pharm Res*. 2015;5:3202-3209.
- Sharma KD, Goswami DS, Seth M, Kashyap S, Daliwal H, Uppal N. Preparation and characterization of enteric coated mucoadhesive tablet of captopril. *J Drug Deliv Ther*. 2013;3:30-36.
- Gadad AP, Reddy AD, Dandagi PM, Masthiholimath VS. Design and characterization of hollow/porous floating beads of captopril for pulsatile drug delivery. *Asian J Pharm*. 2012;6:137.
- Nihar S, Patel K. Design and development of controlled porosity osmotic tablets of captopril. *J Pharm Sci BioSci Res*. 2013;3:145-150.
- Seta Y, Higuchi F, Kawahara Y, Nishimura K, Okada R. Design and preparation of captopril sustained-release dosage forms and their biopharmaceutical properties. *Int J Pharm*. 1988;41:245-254.
- Bera H, Boddupalli S, Nayak AK. Mucoadhesive-floating zinc-pectinate-sterculia gum interpenetrating polymer network beads encapsulating ziprasidone HCl. *Carbohydr Polym*. 2015;131:108-118.
- Diós P, Nagy S, Pál S, Pernecker T, Kocsis B, Budán F, et al. Preformulation studies and optimization of sodium alginate based floating drug delivery system for eradication of *Helicobacter pylori*. *Eur J Pharm Biopharm*. 2015;96:196-206.
- Pawar HA, Lalitha K, Ruckmani K. Alginate beads of captopril using galactomannan containing Senna tora gum, guar gum and locust bean gum. *Int J Biol Macromol*. 2015;76:119-131.
- Chen YC, Ho HO, Liu DZ, Siow WS, Sheu MT. Swelling/floating capability and drug release characterizations of gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose. *PLoS one*. 2015;10:e0116914.
- Kumar Giri T, Verma S, Alexander A, Badwaik H, Krishna Tripathi D. Prospective and new findings of hydroxypropyl methylcellulose (HPMC) as a potential carrier for gastroretentive drug delivery systems. *Drug Deliv Lett*. 2012;2:98-107.
- Pahwa R, Saini N, Kumar V, Kohli K. Chitosan-based gastroretentive floating drug delivery technology: an updated review. *Expert Opin Drug Deliv*. 2012;9:525-539.
- Chen YC, Ho HO, Chiu CC, Sheu MT. Development and characterization of a gastroretentive dosage form composed of chitosan and hydroxyethyl cellulose for alendronate. *Drug Des Devel Ther*. 2014;8:67-78.
- Kajale AD, Chandewar AV. Recent advancement in gastroretentive drug delivery system- a review. *Indo Am J Pharm Res*. 2013;3:5221-5232.
- N Abduljabbar H, M Badr-Eldin S, M Aldawsari H. Gastroretentive ranitidine hydrochloride tablets with combined floating and bioadhesive properties: factorial design analysis, in vitro evaluation and in vivo abdominal x-ray imaging. *Curr Drug Deliver*. 2015;12:578-590.
- G M, Kavitha K, Kumar MR, Singh SJ. Novel mucoadhesive polymers - a review. *J Appl Pharm Sci*. 2011;1:37-42.
- Bhanja SB, Ellaiah P, Martha SK, Kar RK, Panigrahi BB. Buccoadhesive drug delivery system of captopril: formulation and in vitro evaluation. *J Pharm Res*. 2010;3:335-340.
- McElnay JC, al-Furaih TA, Hughes CM, Scott MG, Elborn JS, Nicholls DP. The effect of pH on the buccal and sublingual absorption of captopril. *Eur J Clin Pharmacol*. 1995;48:373-379.
- Emami J, Tavakoli N, Movahedian A. Formulation of sustained-release lithium carbonate matrix tablets: influence of hydrophilic materials on the release rate and in vitro-in vivo evaluation. *J Pharm Pharm Sci*. 2004;7:338-344.
- Akhgari A, Abbaspour MR, Rezaee S, Kuchak A. Evaluation of swelling, erosion and drug release from polysaccharide matrix tablets based on pectin and inulin. *Jundishapur J Nat Pharm Prod*. 2011; 6(1): 51-58.
- Mohammadi-Samani S, Bahri-Najafi R, Yousefi G. Formulation and in vitro evaluation of prednisolone

- buccoadhesive tablets. *Il Farmaco*. 2005;60(4): 339-344.
28. Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and in vitro, in vivo evaluation of extended-release matrix tablet of zidovudine: influence of combination of hydrophilic and hydrophobic matrix formers. *AAPS PharmSciTech*. 2006;7:E1-E9.
 29. Ritger PL, Peppas NA. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. *J Control Rel*. 1987;5:37-42.
 30. Katsuno E, Tahara K, Takeuchi Y, Takeuchi H. Orally disintegrating tablets prepared by a co-processed mixture of micronized crospovidone and mannitol using a ball mill to improve compactibility and tablet stability. *Powder Technol*. 2013;241: 60-66.
 31. Levina M, Rajabi-Siahboomi AR. An industrial perspective on hydrophilic matrix tablets based on hydroxypropyl methylcellulose (Hypromellose). In: Timmins P, Pygall SR, D.Melia C, editors. *Hydrophilic matrix tablets for oral controlled release*. 1st ed. New York: Springer-Verlag; 2014. pp. 53-85.
 32. Bamba M, Puisieux F, Marty JP, Carstensen J. Release mechanisms in gel forming sustained release preparations. *Int J Pharm*. 1979;2:307-315.
 33. Capan Y, Senel S, Calis S, Takka S, Hincal A. Formulation and in vitro-in vivo evaluations on sustained release acetylsalicylic acid tablets. *Pharm Ind*. 1989;51:443-448.
 34. Peppas NA, Sahlin JJ. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *Int J Pharm*. 1989;57:169-172.
 35. Jelvehgari M, Zakeri-Milani P, Khonsari F. Comparative study of in vitro release and mucoadhesivity of gastric compacts composed of multiple unit system/bilayered discs using direct compression of metformin hydrochloride. *Bioimpacts*. 2014;4:29-38.
 36. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. *J Control Rel*. 1985;2:257-275.
 37. Castro del Castillo A, Rodriguez M, Gonzalez E, Rodriguez F, Estruch J. Dose-response effect of sublingual captopril in hypertensive crises. *J Clin Pharmacol*. 1988;28(7):667-670.